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Unspecified stress disorders and risk of arterial and venous thromboembolic disease in the Danish population

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Abstract

Background: Posttraumatic stress disorder is a well-documented risk factor for cardiovascular disease. Whether non-specific stress-related psychopathology also increases risk is less well known.

Methods: In a cohort of adult Danish-born residents of Denmark with an incident diagnosis of unspecified reaction to severe stress ("unspecified stress reaction") between 1995 and 2011 (*N*=24,534), we assessed incidence of seven arterial and venous cardiovascular events/conditions between 1996 and 2013. We calculated standardized incidence ratios (*SIR*s) comparing incidence of each outcome among the cohort to expected incidence based on sex-, age-, and calendar-time-specific national rates. We conducted stratified analyses by demographic characteristics, comorbidities, and length of follow-up time.

Results: Incidence over the study period ranged from 1.1% for provoked VTE to 5.7% for stroke, adjusting for competing risk of death. Unspecified stress reaction was associated with all outcomes (*SIR*s ranging from 1.3, 95% confidence interval (CI): 1.1–1.4 for atrial fibrillation/flutter to 1.9, 95% CI: 1.7–2.2 for unprovoked VTE and 1.9, 95% CI: 1.6–2.3 for provoked VTE). Associations persisted, but were attenuated, when restricting to persons without alcohol use disorder and to persons without physical health comorbidities.

Limitations: Unspecified stress reaction has less precise criteria than other stress-related diagnoses, and we could not adjust for some potential confounders.

Conclusions: Our results augment literature on stress disorders and cardiovascular disease by highlighting the additional importance of unspecified stress disorders. Further research on this diagnostic category, which may represent subsyndromal psychopathology, is warranted. These findings support considering persons with non-specific stress-related psychopathology in treatment and tertiary prevention activities.

Keywords

Cardiovascular; Epidemiology; Stress disorders; Subsyndromal psychiatric disorders; Unspecified reaction to severe stress; Unspecified stress disorders

INTRODUCTION

Psychiatric research is increasingly focused on broad spectrums of psychopathology, no longer limited to disorders that fall within strict diagnostic boundaries (Insel et al., 2010). Persons with subsyndromal posttraumatic stress disorder (PTSD) are similar to those who meet full diagnostic criteria for PTSD in terms of prevalence of depression and functional impairment (Pietrzak et al., 2012b), and risk of death (Gradus et al., 2015a). A small body of literature suggests subsyndromal PTSD is associated with certain specific cardiovascular conditions (e.g., angina (Pietrzak et al., 2012a, 2011) and subclinical atherosclerosis (Holmstrup et al., n.d.)), though not general heart disease (broadly defined) (El-Gabalawy et al., 2018). Research on subsyndromal PTSD and cardiovascular disease (CVD) builds upon well-documented associations between PTSD and CVD (Edmondson and von Känel, 2017; Koenen et al., 2017; Sumner et al., 2015), and recent findings that adjustment disorder (another stress-related diagnosis) is associated with CVD as well (Gradus et al., 2015b; Song et al., 2019).

This study aimed to enhance the limited literature on non-specific stress-related psychopathology (including potentially mild disorders). In a prospective cohort based in Danish national medical and social registries, we investigated the association of the International Classification of Diseases, Tenth Revision [ICD-10] diagnostic category, "unspecified reaction to severe stress," with incidence of seven arterial and venous cardiovascular events/conditions. While all scenarios under which the unspecified reaction to severe stress diagnosis is assigned have not been explicated, it is possible persons receiving this diagnosis had some symptoms consistent with a stress disorder without meeting full diagnostic criteria for any specified disorder (i.e., that they had a subsyndromal stress disorder). We hypothesized that the incidence of myocardial infarction (MI), percutaneous coronary intervention (PCI), heart failure, stroke, atrial fibrillation/flutter, and venous thromboembolism (VTE; provoked and unprovoked) among persons with unspecified reaction to severe stress would be greater than the expected incidence if nationwide age-, sex-, and calendar-time-specific CVD rates applied.

METHODS

Data sources and cohort creation

Data were obtained by linking various registries using the Central Person Registry Number, a unique identifier assigned to all residents and newborns in Denmark (Schmidt et al., 2019). The Danish Civil Registration System (CRS) contains birthdate, sex, demographic data, and up-to-date vital status information for all residents dating back to 1968 (Schmidt et al., 2019). The Danish Psychiatric Central Research Registry (DPCRR) has collected data on inpatient and outpatient psychiatric treatment since 1995, and contains treatment dates and up to 20 diagnoses per treatment episode (Schmidt et al., 2019). The Danish National Patient Registry (DNPR) contains information on all inpatient non-psychiatric hospital treatments in Denmark since 1977, and all outpatient and emergency room visits dating back to 1995 (Schmidt et al., 2019).

The base population was all Danish-born adults aged 16 and older residing in Denmark during any of the period from January 1, 1995, to December 31, 2011 (N = 5,100,339). From the base population, we identified all individuals with an incident ICD-10 diagnosis of F43.9 ("reaction to severe stress, unspecified," henceforth "unspecified stress reaction") recorded in the DPCRR between January 1, 1995, and December 31, 2011 (N=18,662), plus 5,872 individuals with an incident F43.9 diagnosis recorded only in the DNPR (i.e., individuals diagnosed with unspecified stress reaction at a somatic treatment facility only) (total N=24,534). Compared to original medical records, unspecified stress reaction in the DPCRR is reported to have a positive predictive value (PPV) of 68% (Svensson et al., 2015). We excluded emergency room diagnoses of F43.9 due to concerns about diagnostic validity. Patients who received multiple stress disorder diagnoses were categorized according to their primary (i.e., first) incident diagnosis.

Outcomes

Outcomes were incident MI, PCI, heart failure, stroke, atrial fibrillation/flutter, and VTE (provoked and unprovoked) that occurred at least one year after the unspecified stress reaction diagnosis, up to November 30, 2013, as indicated in the DNPR. VTE was considered provoked if the patient had a fracture, surgery, or pregnancy within 90 days before the VTE, or a malignancy any time before the VTE (Cannegieter et al., 2015). PPV for cardiovascular events/conditions in the DNPR is moderate to high (Adelborg et al., 2016; Sundbøll et al., 2016). Patients could have more than one cardiovascular event/condition, and if so, contributed to multiple analyses.

Covariates

Age and sex were obtained from the CRS. As a measure of overall physical health status, we used data from the DNPR to compute a Charlson Comorbidity Index (CCI) score for each cohort member at the time of their unspecified stress reaction diagnosis (Charlson et al., 1987). CCI score was calculated without myocardial infarction, congestive heart failure, or stroke (a subset of cerebrovascular disease), as diagnosis of these conditions at baseline served as exclusion criteria. Finally, we obtained data on depression diagnosis and alcohol abuse/dependence diagnosis (prior to the day of the unspecified stress reaction diagnosis)

from the DPCRR and DNPR. The ICD-8 and ICD-10 codes used to define these conditions are listed in the Appendix.

Analyses

To ensure the unspecified stress reaction diagnosis did not occur after the cardiovascular diagnosis, we restricted our analyses to persons alive and free of all cardiovascular outcomes of interest one year after being diagnosed with unspecified stress reaction.

We calculated the cumulative incidence of each cardiovascular event/condition by the end of the study period among persons with unspecified stress reaction, accounting for death as a competing risk (Gooley et al., 1999). We then calculated standardized incidence ratios (*SIR*s) by dividing the number of observed incident cases by the expected number of incident cases, based on national incidence rates of each outcome. National rates were based on Danish-born residents and were calculated by sex, five-year age group, and five-year calendar period. We multiplied person-years of follow-up by national incidence rates to yield expected case counts. Confidence intervals (CI) were calculated assuming the observed number of cases followed a Poisson distribution.

We conducted stratified analyses by sex, age at unspecified stress reaction diagnosis (16–39, 40–59, and 60+ years), depression diagnosis at baseline, alcohol abuse/dependence diagnosis at baseline, CCI score at baseline, and time interval between unspecified stress reaction diagnosis and cardiovascular event/condition (i.e., length of follow-up; 1 to <5, 5 to <10 and 10+ years).

All statistical analyses were conducted using SAS, version 9.4. The study was approved by the Danish Data Protection Agency (record number 2012–41-0841) and the Institutional Review Board of Boston University.

RESULTS

Almost two-thirds (63%) of the cohort was female. About half of the cohort members (53%) were diagnosed with adjustment disorder at ages 16–39; 37% were diagnosed at ages 40–59; diagnoses at age 60+ were less common (9.5%). Seventeen percent had a prior diagnosis of depression, 14% had a prior alcohol disorder, and 18% had a CCI score of 1 or more (Table 1).

Treating death as a competing risk, the proportion of the unspecified stress reaction cohort that developed each outcome by the end of the study period ranged from 1.1% for provoked VTE to 5.7% for stroke (Table 2). There was an increased incidence of each outcome in the cohort compared to expected incidence based on national sex-, age-, and calendar-time-specific rates (Table 2). The strongest associations were those for unprovoked VTE (*SIR* = 1.9, 95% CI [1.7, 2.2]) and provoked VTE (*SIR* = 1.9, 95% CI [1.6, 2.3]).

For each outcome, the magnitude of the *SIR* decreased with increasing age (Table 2). *SIR*s among those without prior depression, those without a prior alcohol disorder, and those with no prior physical comorbidities tended to be similar to the overall *SIR*s. The persistence of non-null associations among persons without prior depression and persons without prior

alcohol disorders suggested that depression and alcohol disorders were unlikely to be confounders of the associations between unspecified stress reaction and any of the outcomes. However, *SIR*s were near-null for atrial fibrillation/flutter (SIR=1.1, 95% CI: 1.0, 1.2) and PCI (SIR=1.2, 95% CI: 1.0, 1.5), among people with no prior physical comorbidities, suggesting physical comorbidities may be confounders of the associations of unspecified stress reaction with atrial fibrillation/flutter and with PCI (Table 2). In addition, there was evidence of effect measure modification by prior alcohol disorder and prior physical comorbidities, as associations between unspecified stress reaction and several outcomes were stronger among those with an alcohol disorder (versus those without an alcohol disorder) and for those with a CCI score of 1 (versus a CCI score of 0) (Table 2). Finally, there were slight differences in *SIR*s stratified by length of follow-up for stroke and unprovoked and provoked VTE (Table 2).

DISCUSSION

We found that the incidence of seven cardiovascular events/conditions was between 1.3-fold and 1.9-fold higher following diagnosis of unspecified stress reaction, compared to expected incidence based on CVD rates in the general Danish population. These findings are consistent with studies of PTSD (Edmondson and von Känel, 2017; Song et al., 2019; Sumner et al., 2015) and adjustment disorder (Gradus et al., 2015b; Song et al., 2019).

Our results show that various types of stress-related psychopathology, beyond PTSD and adjustment disorder, affect cardiovascular health. There are several possible mechanisms explaining this finding. Stress may lead to behavioral changes, such as substance use or smoking (Edmondson and von Känel, 2017), or to the use of new medications with potential side-effects. Alternatively, stress disorders may cause inflammation, dysregulation of the hypothalamic pituitary adrenal axis, and/or autonomic nervous system dysfunction (Edmondson and von Känel, 2017). While we assessed each cardiovascular outcome individually, they may be interrelated. For example, persons with incident MI may go on to also develop heart failure or atrial fibrillation, and persons with atrial fibrillation are at high risk for stroke. Atherosclerosis may also play a mediating role in some of these relationships.

Our findings on unspecified stress reaction add to a growing understanding of the nature of psychiatric disorders and their treatment. Studying persons with psychopathological symptoms who meet some, but not all, diagnostic criteria for known disorders provides an opportunity to understand the full range of psychopathology that can adversely affect individuals. Persons with non-specific stress-related psychopathology, including subsyndromal and prodromal stress-related disorders, are not often included in treatment trials, and may not be offered standard therapies. However, treating people outside of strict diagnostic boundaries – by taking a staging approach, for example (Mcfarlane et al., 2017) – can substantially reduce the overall burden of stress disorders (Fink et al., 2018).

Our exposure, unspecified stress reaction, likely represents a mixture of persons with subsyndromal stress disorders, prodromal stress disorders, and other situations of which we are not aware. Further research regarding the nature of this diagnosis is warranted. If

unspecified stress reactions represent subsyndromal stress disorders, this diagnosis would provide an opportunity to increase research into subsyndromal stress disorders using administrative/registry data. However, when interpreting the results of the current study, one must be mindful of the possibility that persons who received this diagnosis comprise a potentially heterogeneous group with regard to stress-related symptomology and severity.

Some additional limitations should be considered. First, measurement error was possible. The reported PPV for cardiovascular events/conditions registered in the DNPR is moderate to high (Adelborg et al., 2016; Sundbøll et al., 2016), while the reported PPV for unspecified reaction to severe stress registered in the DPCRR is only 68% (Svensson et al., 2015). Second, we could only assess confounding by one variable at a time via stratification, due to the use of *SIR*s. Third, we could not stratify by certain potential confounders (e.g., socioeconomic status, education, obesity, smoking, moderate substance use, exercise habits), due to the constraints of medical registry data and the dataset used for the present analysis. Fourth, in stratified analyses, each *SIR* is weighted by the distribution of that stratum's person-time, and thus standardized to a slightly different population, meaning comparisons across strata and between different outcomes may be confounded by differences in underlying reference populations.

Despite limitations, our work adds to limited literature suggesting a broad spectrum of stress-related psychopathology – including non-specific diagnoses – can affect cardiovascular health.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Highlights

- Unspecified reaction to severe stress is associated with cardiovascular diseases.

- Incidence of 7 events/conditions is 1.3–1.9 times that in the general population.

- Results are consistent with those observed for posttraumatic stress disorder.

- This disorder category may represent subsyndromal stress disorders.

Table 1.

Characteristics of the unspecified stress reaction cohort (N = 24,534)

	n	%
Sex		
Male	9,005	37
Female	15,529	63
Age at diagnosis		
16–39	13,081	53
40–59	9,124	37
60+	2,329	9.5
Depression[1]	4,069	17
Alcohol abuse/dependence[1]	3,376	14
Components of Charlson comorbidity index (CCI)[1]		
Peripheral vascular disease	201	0.8
Cerebrovascular disease[2]	232	1.0
Dementia	83	0.3
Chronic pulmonary disease	1,578	6.4
Connective tissue disease	473	1.9
Ulcer disease	476	1.9
Mild liver disease	261	1.1
Diabetes	500	2.0
Diabetes with end organ damage	213	0.9
Hemiplegia	55	0.2
Moderate to severe renal disease	193	0.8
Metastatic solid tumor	127	0.5
Non-metastatic solid tumor	1,026	4.2
Leukemia	36	0.2
Lymphoma	87	0.4
Moderate to severe liver disease	51	0.2
AIDS	33	0.1
CCI score 1[3]	4,472	18

[1] Indicates depression, alcohol abuse/dependence, and comorbidities at the time of unspecified stress reaction diagnosis

[2] In this table, cerebrovascular disease excludes stroke.

[3] CCI score calculated without myocardial infarction, congestive heart failure, and stroke (a subset of cerebrovascular disease) as these are outcomes in this analysis, and diagnosis of these conditions at baseline served as exclusion criteria.

Table 2.

Risk of cardiovascular events and conditions among persons diagnosed with an unspecified stress reaction, and standardized incidence ratios[1] comparing risk in the unspecified stress reaction cohort versus the Danish population

	Myocardial infarction	PCI	Heart failure	Stroke	Atrial fibrillation/ flutter	Unprovoked VTE	Provoked VTE
Risk, %[2] (95% CI)	2.9 (2.4, 3.6)	2.2 (1.9, 2.7)	4.1 (3.1, 5.4)	5.7 (5.0, 6.5)	5.2 (4.3, 6.1)	2.2 (1.8, 2.6)	1.1 (0.9, 1.4)
Observed count	272	204	318	499	403	203	121
Expected count	184	149	201	301	321	105	63.1
Overall *SIR*s (95% CI)	1.5 (1.3, 1.7)	1.4 (1.2, 1.6)	1.6 (1.4, 1.8)	1.7 (1.5, 1.8)	1.3 (1.1, 1.4)	1.9 (1.7, 2.2)	1.9 (1.6, 2.3)
Stratified *SIR*s (95% CI)							
Sex							
Women	1.4 (1.2, 1.7)	1.6 (1.3, 1.9)	1.6 (1.4, 1.9)	1.5 (1.4, 1.7)	1.3 (1.1, 1.5)	1.9 (1.5, 2.2)	1.8 (1.4, 2.2)
Men	1.5 (1.3, 1.8)	1.3 (1.0, 1.5)	1.6 (1.4, 1.9)	1.8 (1.6, 2.1)	1.2 (1.1, 1.4)	2.1 (1.7, 2.6)	2.2 (1.6, 2.9)
Age							
16–39 years	2.3 (1.7, 3.1)	2.4 (1.7, 3.2)	2.0 (1.3, 2.8)	1.9 (1.5, 2.4)	1.7 (1.2, 2.2)	2.3 (1.9, 2.9)	2.6 (1.8, 3.5)
40–59 years	1.4 (1.2, 1.7)	1.3 (1.1, 1.5)	1.8 (1.5, 2.1)	1.8 (1.6, 2.1)	1.3 (1.1, 1.5)	1.9 (1.5, 2.3)	2.0 (1.5, 2.6)
60+ years	1.3 (1.0, 1.6)	1.2 (0.8, 1.6)	1.4 (1.2, 1.6)	1.4 (1.2, 1.6)	1.1 (1.0, 1.3)	1.5 (1.0, 2.1)	1.3 (0.8, 1.9)
Depression							
No	1.4 (1.3, 1.6)	1.4 (1.2, 1.6)	1.6 (1.4, 1.8)	1.6 (1.5, 1.8)	1.3 (1.2, 1.4)	1.9 (1.6, 2.2)	2.0 (1.6, 2.4)
Yes	1.6 (1.2, 2.2)	1.4 (1.0, 2.0)	1.6 (1.2, 2.0)	1.9 (1.5, 2.3)	1.1 (0.9, 1.4)	2.3 (1.6, 3.2)	1.7 (1.0, 2.7)
Alcohol abuse/ dependence							
No	1.4 (1.3, 1.6)	1.4 (1.2, 1.6)	1.5 (1.3, 1.8)	1.5 (1.3, 1.6)	1.2 (1.0, 1.3)	1.7 (1.5, 2.0)	1.8 (1.4, 2.1)
Yes	1.7 (1.3, 2.3)	1.1 (0.8, 1.6)	2.3 (1.8, 3.0)	2.9 (2.4, 3.5)	1.9 (1.5, 2.4)	3.2 (2.3, 4.3)	3.0 (2.0, 4.5)
CCI score[3]							
0	1.3 (1.2, 1.5)	1.2 (1.0, 1.5)	1.3 (1.1, 1.5)	1.5 (1.4, 1.7)	1.1 (1.0, 1.2)	1.9 (1.6, 2.3)	1.7 (1.3, 2.1)
1	1.9 (1.5, 2.4)	1.8 (1.4, 2.3)	2.4 (2.0, 2.8)	2.1 (1.8, 2.5)	1.7 (1.5, 2.0)	2.0 (1.4, 2.7)	2.8 (2.0, 3.7)
Length of follow-up							
1 to <5 years	1.5 (1.3, 1.8)	1.3 (1.0, 1.6)	1.5 (1.3, 1.8)	1.6 (1.4, 1.9)	1.2 (1.0, 1.4)	2.0 (1.6, 2.4)	2.2 (1.7, 2.9)
5 to <10 years	1.6 (1.3, 1.9)	1.4 (1.1, 1.8)	1.6 (1.3, 1.9)	1.5 (1.3, 1.8)	1.4 (1.2, 1.6)	1.7 (1.3, 2.2)	1.8 (1.3, 2.4)

	Myocardial infarction	PCI	Heart failure	Stroke	Atrial fibrillation/ flutter	Unprovoked VTE	Provoked VTE
10+ years	1.3 (0.9, 1.7)	1.5 (1.1, 2.0)	1.8 (1.4, 2.2)	2.0 (1.7, 2.4)	1.3 (1.0, 1.5)	2.3 (1.7, 3.1)	1.5 (0.9, 2.3)

SIR, standardized incidence ratio; CI, confidence interval; PCI, percutaneous coronary intervention; VTE, venous thromboembolism

[1] Adjusted for sex, five-year age group, and five-year calendar period.

[2] Risk is absolute risk of each cardiovascular event/condition among the unspecified stress reaction cohort by the end of follow-up, treating death as a competing risk.

[3] CCI score calculated without myocardial infarction, congestive heart failure, or stroke, as these are outcomes of interest and diagnosis of these conditions at baseline served as exclusion criteria.